REMARKS/ARGUMENTS

Prior to the present amendments, claims 11-18 were pending in this application. Claims 11 and 15-18 have been canceled, without prejudice or disclaimer, claims 12-14 are rejected. Applicants specifically reserve the right to pursue any canceled subject matter in one or more divisional and/or continuation application.

Claim Rejections – 35 U.S.C. § 101

The sole rejection remaining in this application is the maintained rejection of claims 12-14 under 34 U.S.C. § 101 on the ground that the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility for the isolated polypeptide.

The claims are drawn to methods of enhancing the infiltration of immune cells in a mammal (claims 12 and 13) and methods of alleviating infection in a mammal by administering an effective amount of the Bolekine polypeptide of SEQ ID NO: 2 (claim 14). The immune stimulatory activity of Bolekine, and consequently the use of the Bolekine in the claimed methods, is supported by the enhancement of mixed lymphocyte reaction (MLR) by Bolekine (Example 10) and the activity in the Skin Vascular Permeability Assay (Example 11). The disagreement between Applicants and the Examiner is in the value of these data and, in particular, whether the results obtained in these assays are sufficient to establish a real-life utility. Applicants submit that they are, and respectfully traverse the rejection.

The MLR Assay

In her critique of the MLR assay results in the Office Action mailed on July 27, 2005, referenced on page 3 of the present Office Action, the Examiner states that: (1) the specification fails to teach where an enhancement of an immune response is beneficial and therapeutically useful; (2) the ability to stimulate or inhibit lymphocyte Bolekine proliferation in the MLR assay is an artificial *in vitro* system and does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function; (3) the MLR reaction is not predictive of general responses of the immune system since *in vivo* activation of a lymphocyte is controlled not only by antigen binding but also by interactions with other cells; (4) Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; and (5) the statement that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be

beneficial is not specific since there are many such conditions, and it is not predictable of which conditions the claimed invention may function.

Starting with the issue whether the specification teaches where the enhancement of an immune response is beneficial and therapeutically useful, it is well established that information which is well known in the art does not have to be described in detail in the specification. As it is explained in MPEP Section 601:

> "Where elements or groups of elements, compounds, and processes, which are conventional and generally widely known in the field to which the invention pertains, form a part of the invention described and their exact nature or type is not necessary for an understanding and use of the invention by a person skilled in the art, they should not be described in detail."

At the time the present application was filed, one of ordinary skill would have clearly been able to identify conditions where the enhancement of immune response is beneficial. Thus, at the effective filing date of this application it was known that HIV-1 positive and AIDS patients benefit from the enhancement of their immune response which facilitates their defense against opportunistic infections (McElrath et al., Proc. Natl. Acad. Sci. USA 87(15):5783-7 (1990) – copy enclosed). It was also known that other patients with opportunistic infections, such as multidrug-resistant tuberculosis benefit from immune stimulatory therapy (McDyer et al., J. Immunol. 158(1):492-500 (1997) – copy enclosed), and the stimulation of immune response is beneficial in the treatment of various malignancies, including cutaneous T cell lymphoma (Zaki et al., J. Invest. Dermatol. 118(2):366-71 (2002) – copy enclosed) and viral infections, such as genital and perianal warts (Tyring, S., Skin Therapy Lett. 6(6):1-4 (2001) – copy enclosed). Accordingly, the statement at page 87, lines 5-6 that "[c]ompounds which stimulate proliferation of lymphocytes [in the MLR assay] are useful therapeutically where enhancement of an immune response is beneficial" would have been understood by those skilled in the pertinent art, without the need for any further explanation.

Furthermore, contrary to the Examiner's assertion, the statement that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial is specific. The fact there are many conditions benefiting from the claimed invention has absolutely no bearing on the specificity of this utility. In addition, the claims are not directed to Bolekine polypeptides or the treatment of conditions where the enhancement of immune response in general would be beneficial. Claims 12 and 13 specify

methods directed to the enhancement of the infiltration of immune cells in a mammal, and it is clear that any condition that is characterized by the suppression of immune response, such as immune related disorders (claim 14) would expected to benefit from such infiltration.

Applicants also strongly disagree with the Examiner's criticism of the MLR assay. It is well established that the MLR assay is an art accepted assay for identifying immune suppressive molecules and the assay is generally predictive of their *in vivo* effectiveness (see column 12, lines 36-41 of U.S. Patent No. 5,817,306 – copy enclosed). Similarly, the MLR assay has been used and relied on by those of ordinary skill in the art to identify immunostimulatory compounds, or to confirm the immunoenhancing activity of compounds using this assay. Thus, for example, Dziarski, R., J. Immunol. 143(1):356-365 (1989) (copy enclosed) used this assay to show that heparin and various heparinoids have immunoenhancing properties, and note that such responses might be beneficial in increasing host responses against viral infections and tumors (page 364, last paragraph).

Thus, the use of the MLR assay is well established for the identification of immunomodulatory compounds, including compounds that stimulate and compounds that stimulate (enhance) the immune response. Dziarski et al. and U.S. Patent No. 5,817,306 also establish that those skilled in the art have no difficulty correlating results obtained in this assay with real-life clinical uses, in the treatment of a series of very serious diseases and conditions.

Accordingly, it is submitted that the MLR assay results set forth in Example 10 alone are sufficient to establish a credible, specific and substantial asserted utility for the Bolekine polypeptide of the present invention, and, as a result, support the utility of the methods claimed in pending claims 12-14.

In further support of their position concerning the MLR assay, Applicant submitted a Declaration by Dr. Sherman Fong. While the Examiner acknowledges that "Applicant states that in support of the MLR assay and the Vascular Permeability Assay, a declaration under 37 CFR 1.132 from Dr. Sherman Fong has been submitted," in the analysis following this statement, the Examiner's analysis is limited to the Declaration dealing with the Vascular Permeability Assay. The make the record clear, with the response mailed on October 16, 2005 (and received in the USPTO on October 28, 2006) Applicants submitted two Declarations by Dr. Fong, one concerning the MLR assay, and one the Vascular Permeability Assay. The Examiner has given no reasons by the Fong Declaration concerning the MLR assay has not been found convincing.

Dr. Fong is an inventor of the above-identified patent application, and an experienced scientist familiar with the MLR assay, which was used by him and others under his supervision, to test the immune stimulatory or immune inhibitory activity of novel polypeptides discovered in Genentech's Secreted Protein Discovery Initiative project, including PRO1375.

The Fong Declaration explains how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs), which contain responder T-cells, and allogenic, pre-treated (irradiated) PBMCs, which predominantly contained dendritic cells. Dr. Fong proceeds to explain (paragraph 7 of the Declaration) that dendritic cells are potent antigen-presenting cells that are able to "prime native T cells *in vivo*." Once activated by dendritic cells, the T-cells are capable of interacting with other antigen-presenting cells (B cells and macrophages) to produce additional immune responses from these cells.

As Dr. Fong states, the MLR assay of the present application

> is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR, and thus identifies immune stimulants that can boost the immune system to respond to a particular antigen that may not have been immunologically active previously. (Paragraph 8 of the Fong Declaration.)

As Dr. Fong emphasizes, immunostimulants are important and highly desirable in the treatment of cancer and in enhancing the effectiveness of previously identified treatments for cancer.

In paragraph 9 of his Declaration, Dr. Fong provides examples of important clinical applications for immune stimulants which have been shown to stimulate T-cell proliferation in the MLR assay. As Dr. Fong explains,

> "IL-12 is a known immune stimulant, which has been shown to stimulate T-cell proliferation in the MLR assay. IL-12 was first identified in just such an MLR [Gubler, et al. PNAS 88, 4143 (1991) (Exhibit C)]. In a recent cancer vaccine trial, researchers from the University of Chicago and Genetics Institute (Cambridge, MA) have demonstrated the efficacy of the approach, relying on the immune stimulatory activity of IL-12, for the treatment of melanoma. [Peterson, et al. Journal of Clinical Oncology 21 (12); 2342-48 (2003) (Exhibit D)] They extracted circulating white blood cells carrying one or more markers of melanoma cells, isolated the antigen, and returned them to the patients. Normally patients would not have an immune response to his or her own human antigens. The patients were then treated with different doses of IL-12, an immune stimulant capable of inducing the proliferation of T cells that have been co-stimulated by dendritic cells. Due to the immune stimulatory effect of IL-12, the treatment provided superior results in comparison to earlier work, where patients' own dendritic cells were prepared from peripheral blood mononuclear cells (PBMCs), treated

with antigens, then cultured *in vitro* and returned to the patient to stimulate anti-cancer response. [Thurner, et al. J. Exp. Med. 190 (11); 1669-78 (1999) (Exhibit E)]."

Dr. Fong concludes that (paragraph 10):

> It is my considered scientific opinion that a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant."

Accordingly, the positive results obtained in this assay clearly establish the immunostimulant utility for the Bolekine polypeptide, used in the methods of the present invention, and the specification.

The Skin Vascular Permeability Assay

In addition, Applicants maintain that the skin vascular permeability assay further supports the utility of the methods claimed in the present application. In support of the relevance of this assay and the results obtained by it, Applicants submitted a second Declaration by Dr. Sherman Fong. According to the Office Action, this Declaration "has been fully considered but is not found sufficient to overcome the rejection." The Examiner notes that this "assay [also known as the Miles assay] is useful as a preliminary screen for potential proinflammatory molecules," but "further work must be done subsequent to a positive result in a Miles assay to determine if and how a molecule may be useful as a proinflammatory." The Examiner adds that "[b]asic irritants, such as lye, would test positive in the Miles assay," notes that the Declaration is not specific for the Bolekine polypeptides of the present invention and "the assay does not provide the skilled artisan with the guidance necessary for the skilled artisan to determine how to use the claimed PRO polypeptide without resorting to undue experimentation. With regard to Dr. Fong's statement that the PRO polypeptides that tested positive in this assay were further analyzed by hitopathological examination to rule out inflammation due to endothelial cell damage or mast cell degranulation, the Examiner notes that this statement is not entirely correct, since it is contradicted with the specification.

First of all, Applicants maintain that the MLR assay alone is sufficient to establish patentable utility for the claimed methods.

Secondly, the fact that further work might be needed to further confirm a positive result in the Miles assay is not a sufficient reason to conclude that the assay cannot establish patentable utility. If an

assay, like the Miles assay, shows a good general correlation with a real-life practical use (see the second Fong Declaration), the fact that further confirmatory tests might be necessary before a compound put to that practical use are of no relevance for patentability.

Thirdly, the comment on undue experimentation is misplaced, since determination if undue experimentation is necessary practice a claimed invention is not part of the assessment of compliance with the utility requirement of 35 USC 101.

Finally, the statement that "the Declaration is not entirely correct with respect to the facts" is misplaced. The Daclaration, Dr. Fong, has first hand knowledge about how the test was performed. If there is any perceived discrepancy between his description of the test and the description provided in the specification, such disagreement should be reasonably resolved by accepting Dr. Fong's description.

In conclusion, it is submitted that the MLR assay results alone are sufficient to establish that the utility requirement of 35 USC 101 has been met, and the skin vascular permeability assay further supports this conclusion. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Claim Rejections – 35 U.S.C. § 112, first paragraph, Enablement

Claims 12-14 remain rejected under 35 U.S.C. 112, first paragraph, since "the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention."

In response to the rejection under 35 USC 101 above, Applicants has shown that the claimed invention is supported by a credible, specific and substantial asserted utility, accordingly the present rejection should be withdrawn.

Please charge any fees that might become applicable, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1192-2C1). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

(Panpan Guo 43,626) on behalf of Ginger Dreger

Date: October 17, 2006

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